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Allogeneic Peripheral Blood Stem Cell Transplant in Children

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Allogeneic peripheral blood stem cell (PBSC) transplant has recently been introduced for the treatment of hematological malignancies. As the data were limited mainly to adult patients, this study aimed to assess the feasibility and safety of this procedure in pediatric patients and donors. Eleven children aged 2–16 years received allogeneic PBSC transplant for acute lymphoblastic leukemia (n = 4), acute myeloid leukemia (n = 1), myelodysplastic syndrome (n = 1), severe aplastic anemia (n = 3), and thalassemia (n = 2). Nine donors were human leukocyte antigen (HLA)-identical siblings and the other two were one antigen mismatched family members. Eight donors were younger than 18 years old (10 months to 17 years). Donors were primed with granulocyte colony-stimulating factor (G-CSF) at 10–16 μg/kg for 4–5 days. Aphereses were performed on 1 or 2 consecutive days, and the patients received a mean of 14.4 × 10^8/kg nucleated cells, 6.9 × 10^6/kg CD34 cells, and 6.9 × 10^8/kg T cells. All patients achieved neutrophil counts of >0.5 × 10^9/l at a median of 16 days. Nine patients achieved platelet counts of >20 ×10^9/l at a median of 13 days. Grade II acute graft vs. host disease (GVHD) occurred in only one patient. Chronic GVHD was not observed in the seven patients with follow-up of more than 3 months. Eight patients remained in continuous complete remission after transplant ranged from 2 to 26 months. Allogeneic PBSC transplant appears safe in pediatric patients and donors, and it seems not to be associated with increase of acute GVHD or chronic GVHD. Med. Pediatr. Oncol. 30:147–151, 1998.

Key words: peripheral blood stem cell transplant; G-CSF priming; normal donors

INTRODUCTION

Hematopoietic stem cells can be mobilized into the peripheral circulation after chemotherapy. With the use of growth factors, large quantities of peripheral blood stem cells (PBSC) can be collected for rescue therapy after myeloablative treatment. Autologous PBSC transplant has been reported for more than 10 years [1], but only in recent years have the applications of PBSC transplant in allogeneic settings been studied [2–4]. The data on pediatric patients and donors are very limited [5]. Allogeneic PBSC transplantation has the advantages of more rapid engraftment and less treatment-related toxicity. It also has the advantage of avoiding general anesthesia and bone marrow harvest in donors. The number of cases reported is rapidly increasing, but these reports are nearly all limited to adult patients. In young children, venous access and small blood volume are common technical problems which need special attention. Compared to adults, children are known to have higher T-cell numbers in peripheral blood, and young children have a higher CD4/CD8 ratio [6]. Whether the differences in T-cell numbers may have an effect on the incidence or severity of graft vs. host disease (GVHD) is unknown. We report 11 pediatric patients treated by allogeneic PBSC transplant, in whom 8 of the PBSC donors were children.

PATIENTS AND METHODS

Children with malignant and severe hematological diseases requiring allogeneic bone marrow transplant (BMT) were offered either bone marrow (BM) or PBSC as a source of stem cells for transplant. Details of the procedure and risk of granulocyte colony-stimulating factor (G-CSF; Filgrastim, Roche, Basel, Switzerland) were fully explained. Nine of the donors were human leukocyte antigen (HLA)-identical siblings and two were one antigen mismatched family members (father and sis-

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TABLE I. Patient and Donor Characteristics*

Patient no.	Patient's sex/age (years)	Donor's sex/age	Patient/donor weight (kg)	HLA typing	Disease	Indication for transplant	Dose (μg/kg) of G-CSF
1	F/12	F/17 years	32.5/49.6	ID-sib	Aplastic anemia/ thalassemia	Pancytopenia	12 × 4 days
2	M/2.5	F/10 months	13.2/8.7	ID-sib	ALL, CR1	Ph chromosome	16 × 5 days
3	M/8	M/11 years	21.6/27.6	ID-sib	ALL, CR1	WBC 235 × 10^9/l T-cell, t(11;14)	16 × 5 days
4	M/2	M/11 years	12.9/42.9	ID-sib	ALL, CR1	WBC 153 × 10^9/l t(1;19)	14 × 5 days
5	F/15	F/31 years	60.5/66.4	ID-sib	ALL, CR3	Relapsed ALL	10 × 5 days
6	M/16	F/19 years	35/63	ID-sib	Thalassemia	Transfusion dependent	10 × 5 days
7	F/10	F/2 years	28.2/12	ID-sib	Aplastic anemia	Pancytopenia	13 × 5 days
8	F/13	F/16 years	50.2/57	ID-sib	Aplastic anemia	Pancytopenia	10 × 5 days
9	F/3.8	M/36 years	15.1/58.3	1 Ag MM[a]	AML, CR1	AML	10 × 4 days
10	M/6.5	F/14.2 years	21/65.5	ID-sib	Thalassemia	Transfusion dependent	10 × 4 days
11	F/6.2	F/12.5 years	18.5/36.1	1 Ag MM[b]	MDS	RAEB-T	10 × 4 days

*ALL, acute lymphoblastic leukemia; CR, complete remission; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; RAEB-T, refractory anemia with excess blast in transformation; ID-sib, identical sibling; 1 Ag MM, 1 antigen mismatch; WBC, white blood cells.
[a]Father.
[b]Sister.

ter). Informed consent was obtained from parents and from the donors if over 16 years. The study was approved by an institutional ethical committee. Seven donors preferred PBSC instead of BM harvest. PBSC harvest was suggested to two donors because their weights were much less than those of recipients, while the other two were due to medical reasons (scoliosis; two previous BM graft rejections). Patient and donor characteristics are shown in Table I. A thalassemia patient had successful engraftment after first BMT, but had rejection of BM 5 months later. Second BMT was performed for severe marrow aplasia with the same BM donor. Total lymphoid irradiation 2 Gy bid for 3 days at mantle and inverted Y field and etoposide 60 mg/kg was the conditioning regimen, but there was no sign of engraftment on day 21. A third transplant using PBSC from the same donor was done without further conditioning. Four children suffered from acute lymphoblastic leukemia (ALL) and three were transplanted during first complete remission (CR1). They were conditioned with cyclophosphamide 60 mg/kg intravenously (iv) for 2 days and total body irradiation 2 Gy bid for 3 days. One ALL patient in CR3 was conditioned with busulfan 16 mg/kg, etoposide 60 mg/kg, and cyclophosphamide 120 mg/kg. The myelodysplastic syndrome (MDS) patient, refractory anemia with excess blast in transformation (RAEB-T), and an acute myeloid leukemia patient were transplanted in CR1 with busulphan 16 mg/kg and cyclophosphamide 200 mg/kg. Two aplastic anemia patients were transplanted soon after diagnosis with cyclophosphamide 200 mg/kg and antithymocyte globulin 30 mg/kg for 3 days. Two thalassemia patients were conditioned with busulphan 16 mg/kg and cyclophosphamide 150 or 200 mg/kg. Cyclosporin A 3 mg/kg/day iv from day −1 and methotrexate iv on days 1, 3, 6, and 11 were used as prophylaxis against GVHD. GVHD was graded according to standard criteria [7]. Hematological recovery and toxicity were closely monitored. Chimerism study was monitored by fluorescent in situ hybridization and DNA analysis using variable number of tandem repeats (VNTR).

Four days before stem cell transplant, donors were treated with G-CSF at 10–16 μg/kg subcutaneously (sc) daily for 4–5 days. The first PBSC harvest was performed on day 0 of transplant and the second harvest was performed the next day. PBSC were collected by Fenwall CS3000 (Baxter, Deerfield, IL, USA) or Cobe Spectra (COBE BCT, Lakewood, CO, USA) Cell separators. The cell separator was primed with irradiated red cells if the donor's body weight was less than 30 kg. The processing blood volume for each apheresis was targeted at 2 times blood volume. Total nucleated cells, CD34 cells, and T cells (CD3, CD4, CD8) of the PBSC were measured by flow cytometer for each PBSC product. The lysed whole blood method was performed on PBSC samples using FACS lysing solution [Becton Dickinson (BD), San Jose, CA] according to the manufacturer's protocol. The CD45-fluorescein isothiocyanate (FITC) and side scatter profile was used to identify the mononucleated cells and lymphocyte population. A minimum of 75,000 and 10,000 cells were acquired using the LYSIS II software of the FACScan instrument (BD) for the analysis of CD34 and lymphocyte subsets, respectively. The PBSC were infused directly into the patients without any processing on 1 or 2 days. The donors were monitored for daily blood counts during G-CSF treatment and serum electrolytes were also checked before and after each apheresis. The donors would be followed up yearly for blood counts.

TABLE II. PBSC Characteristics*

Patient no.	No. of aphereses	No. of TN × 10^8/kg infused (#1/#2)	No. of CD34 × 10^6/kg infused (#1/#2)	No. of CD3 × 10^8/kg infused (#1/#2)	No. of CD4 × 10^8/kg infused (#1/#2)	No. of CD8 × 10^8/kg infused (#1/#2)
1	2	13.42 (5.29/8.12)	17.04 (6.85/10.19)	ND	ND	ND
2	2	16.06 (7.88/8.18)	4.01 (2.10/1.91)	7.59 (3.80/3.79)	3.95 (1.95/2.0)	3.35 (1.71/1.64)
3	2	32.5 (16.62/15.93)	4.04 (2.84/1.19)	7.31 (3.65/3.66)	2.72 (1.34/1.38)	3.52 (1.76/1.76)
4	2	26.05 (16.74/9.30)	20.43 (14.4/5.99)	15.98 (10.11/5.87)	9.07 (5.53/3.54)	7.33 (4.44/2.89)
5	2	13.71 (11.30/2.41)	5.11 (3.91/1.19)	3.67 (2.50/1.17)	1.59 (1.07/0.52)	1.62 (1.07/0.55)
6	2	7.85 (5.46/2.39)	5.25 (3.69/1.56)	5.04 (3.51/1.53)	2.61 (1.82/0.79)	2.46 (1.73/0.73)
7	2	4.15 (2.08/2.07)	2.17 (1.27/0.90)	2.20 (1.05/1.15)	1.38 (0.67/0.71)	0.82 (0.38/0.44)
8	2	9.73 (5.83/3.9)	3.14 (1.87/1.27)	6.13 (3.74/2.39)	4.20 (2.63/1.57)	2.17 (1.26/0.91)
9	1	12.52	3.56	7.32	3.70	3.36
10	1	13.76	5.66	8.62	4.51	3.81
11	1	8.92	4.93	5.65	3.41	2.19
Mean of infusate ± SD (#1/#2)		14.43 ± 8.2 (9.67/6.83)	6.85 ± 6.01 (4.65/3.0)	6.95 ± 3.72 (5.00/3.09)	3.74 ± 2.16 (2.66/1.65)	3.06 ± 1.77 (2.17/1.41)

*TN, total nucleated cells; #1, first apheresis; #2, second apheresis; ND, not done.

RESULTS

The pediatric donors did not experience any side effects such as fever or bone pain during G-CSF treatment. The adult donors complained of lassitude and mild bone pain during G-CSF treatment which resolved after stopping treatment. Nine donors had their venous access via antecubital veins. The 10-month-old baby had the femoral vein cut down for the procedure and the venous catheter was removed on the next day. A 2-year-old donor had a temporary central venous catheter inserted under general anesthesia. There was no complication during the apheresis procedure. The first eight patients were all scheduled to have two collections, and the last three patients did not require a second harvest because the CD34 cells in a single apheresis were more than 3×10^6/kg. The characteristics of the PBSC products are shown in Table II. The mean total nucleated cells, CD34 cells, and CD3 cells of the infused PBSC per recipient body weight were 14.4×10^8, 6.9×10^6, and 6.9×10^8/kg, respectively. The mean CD4 and CD8 cells were 3.7×10^8 and 3.1×10^8/kg, respectively. The mean CD4/CD8 ratio was 1.2.

The post-transplant outcome is shown in Table III. The patients had absolute neutrophil counts of $>0.5 \times 10^9$/l at a median of 16 days (range 9–21 days). Nine patients achieved platelet independence and had platelet counts of $>20 \times 10^9$/l at a median of 13 days (range 13–87 days) and eight patients $>50 \times 10^9$/l at a median of 15.5 days (range 13–100 days). The first patient who received a third stem cell transplant had initial rapid neutrophil engraftment but did not achieve platelet independence because of concurrent active infection and bleeding. She rejected the PBSC graft on day 50 and finally died 4 months later due to infection. One patient had severe veno-occlusive disease and required frequent platelet support for active bleeding, and he died of idiopathic interstitial pneumonitis on day 28. One patient developed severe hemorrhagic cystitis and pleural effusion which required multiple platelet and red cell transfusion up to day 87. For the other eight patients, they received a median of one red cell transfusion and two platelet transfusions after transplant. One patient developed Respiratory Syncytial virus (RSV) pneumonia on day 4 which responded to ribavarin inhalation. Three patients developed herpes simplex oral mucositis which subsided after acyclovir treatment. The other patients were febrile but none had documented septicemia or identifiable source of infection. Acute GVHD occurred in three patients and involved the skin only (one grade II and two grade I). Two patients received one antigen mismatched transplant, one developed grade I skin GVHD. They responded promptly to steroid treatment. Seven patients have now been followed-up for more than 3 months (range 3–25 months) and none has developed chronic GVHD. Chimerism study was performed on the eight survivors and six showed complete donor chimerism, while two had mixed chimerism and one subsequently relapsed. Cytogenetic study of the three patients with abnormal clones at pre-transplant did not show the original abnormalities post-transplant. Molecular analysis for bcr-abl rearrangement of Ph chromosome was negative. The ALL patients transplanted in third remission had BM relapse 1 year after transplant and died 1 month later. The eight surviving patients were all in hematological remission at a median follow-up of 7 months (range 2–26 months).

DISCUSSION

Allogeneic BMT has been shown to be successful in the treatment of various malignant and non-malignant hematological conditions in children [8,9]. However, treatment-related toxicities carry a significant risk to

TABLE III. Post-Transplant Outcome*

Patient no.	Day ANC		Day Plt		No. of RBC Tx	No. of Plt Tx	Acute GVHD	Infection	Follow-up
	$>0.5 \times 10^9$/l	$>1.0 \times 10^9$/l	$>20 \times 10^9$/l	$>50 \times 10^9$/l					
1	9	10	NE	NE	NE	NE	0	FUO	Rejected PBSC graft on day 50
2	15	16	13	13	1	1	0	FUO	CR, 26 months
3	16	17	13	13	1	1	0	FUO	CR, 24 months
4	13	16	14	16	2	2	II skin	RSV pneumonia	CR, 22 months
5	12	14	14	14	1	5	0	Herpes simplex I	RL 1 year, died
6	13	13	NE	NE	NE	NE	0	FUO	Died day 29, IIP
7	19	22	13	19	3	4	0	FUO	CR, 7 months
8	20	21	87	100	16	27	0	FUO	CR, 7 months
9	21	37	13	15	1	2	0	Herpes simplex I	CR, 3 months
10	18	28	26	NY	4	7	I	FUO	CR, 2 months
11	18	21	13	18	1	2	I	Herpes simplex I	CR, 2 months
Median	16	17	13	15.5	1	2			7 months

*ANC, absolute neutrophil count; Plt, platelet; RBC, red blood cells; Tx, transfusion; NE, not evaluable; FUO, fever of unknown origin; CR, complete remission; RL, relapsed; IIP, idiopathic interstital pneumonitis; NY, not yet.

BMT patients. Prolonged myelosuppression after conditioning leads to life-threatening infection and serious bleeding. Use of growth factors after bone marrow infusion might hasten the neutrophil recovery but has no effect on platelet recovery [10]. Autologous PBSC transplants after mobilization by growth factors have rapid hematopoietic recovery including both neutrophils and platelets [11]. Recently, allogeneic PBSC transplant has been introduced. One of the major concerns about allogeneic PBSC transplant is GVHD. It has been shown that T-cell numbers in PBSC are in general one log increased compared with those in bone marrow [2–4]. Thus there might be the possibility of increased incidence and severity of acute GVHD, but the reported series of allogeneic PBSC transplant have not shown this. In our series of 11 patients, only 1 patient had grade II GVHD. Two patients received one antigen mismatch transplant, and one patient developed grade I GVHD. In our center, the incidence of ⩾grade II acute GVHD in HLA-identical sibling BMT was 26%. PBSC transplant appears not to have higher incidence of acute GVHD. The infused T-cell numbers of our patients were similar to the other adult PBSC series. It has been suggested that T cells mobilized by G-CSF might be different from those of BM and have suppressive effect on GVHD [12]. It has been postulated that acute GVHD is related more to the histocompatibility between the donor and the patient than to the number of T cells. The question of chronic GVHD is not yet solved due to short duration of follow-up and the small number of patients. None of our patients followed for more than 3 months developed chronic GVHD. Rapid hematopoietic recovery was seen in our patients. In most patients, the neutrophil and platelet recovery were rapid and required only a few transfusions (six patients required only one to two red cells and platelet transfusion during the transplant course). The rapid platelet recovery was even more remarkable (seven patients had a platelet count $>50 \times 10^9$/l before day 20). Compared with autologous PBSC transplant, the rate of neutrophil engraftment is slower, which may be related to the use of methotrexate in the GVHD prophylaxis.

The issue of donor safety in receiving growth factors has been of concern in allogeneic PBSC transplant. Some investigators considered the risk of using G-CSF is much less than that of general anesthesia and trauma to the soft tissue and bone [13]. With a few days treatment of G-CSF in normal donors, there has been no report of long-term complications. There are now over 500 patients being transplanted with allogeneic PBSC transplant [14]. There was report of increased incidence of leukemia in patients receiving G-CSF, but that was in the setting of prolonged use of G-CSF in patients with underlying hematological diseases [15]. Experience in autologous PBSC transplant has shown that the procedure of apheresis can be performed safely in young children [16]. Priming the cell separator for children less than 30 kg has eliminated the risk of hemodynamic imbalance in these young children. Homologous blood transfusion may have a potential risk of transmitting infection to the donors. In Hong Kong, all children are immunized with hepatitis B vaccine at birth and the carrier rate of human immunodeficiency virus (HIV) among blood donors is very low. The risk of transfusion-transmitted infection is further reduced by careful screening of the blood units. Venous access can be a technical problem in young children. Using larger veins at the antecubital region is possible in most young children, and for very young children and babies, percutaneous puncture or cut down of the femoral vein can avoid an operation for central venous catheter insertion. Radial artery catheterization has also been shown to be adequate for PBSC collection in young children [17].

In conclusion, allogeneic PBSC transplant is feasible in children. As in adult series, PBSC transplant is associated with rapid engraftment without increase in acute

GVHD. Pediatric donors tolerated the mobilization and PBSC collection well. The cost benefit of pediatric allogeneic PBSC transplant needs further evaluation.

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